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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,008	04/12/2001	Shinichi Mochizuki	10939/2022	4949

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,008	MOCHIZUKI ET AL.	
	Examin r	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/20/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 6-32 are pending.

Applicants' amendment filed July 29, 2003 is acknowledged, and applicants' response has been fully considered. Claims 1-5 have been cancelled, and new claims 6-32 have been added. Therefore, claims 6-32 are examined.

Foreign Priority

2. A certified copy of JP 322874/1998 application filed July 29, 2003 is acknowledged.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 1-4, under 35 U.S.C.112, first paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed July 29, 2003.

4. The previous rejection of claims 1-5, under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' cancellation of the claim, and applicants' response at page 7 of the amendment filed July 29, 2003.

Claim Rejections - 35 USC § 102

5. The previous rejection of claims 1 and 2 under 35 U.S.C. 102(a) as being anticipated by Goto *et al.* (EP 0816380, January 7, 1998), is withdrawn in view of applicants' cancellation of the claim, and applicants' response at page 8 of the amendment filed July 29, 2003.

6. The previous rejection of claims 1, 3 and 4 under 35 U.S.C. 102(a) as being anticipated by Goldenberg *et al.* (WO 98/46211, October 22, 1998), is withdrawn in view of applicants' cancellation of the claim in the amendment filed July 29, 2003.

7. The previous rejection of claims 1, 3 and 4 under 35 U.S.C. 102(b) as being anticipated by Goto *et al.* (EP 0816380, January 7, 1998), is withdrawn in view of applicants' cancellation of the claim, and applicants' response at page 10 of the amendment filed July 29, 2003.

Claim Objection

8. Claims 8, 16, 22 and 28 are objected to because a misspelled word "chondoroitin".

9. Claims 12 and 32 are objected to because a misspelled word "osteoporsis".

10. Claim 24 is objected to because the claim recites the heparin having a molecular weight of "3,00" to 6,000, which should be 3,000 to 6,000.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 6-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 7-13, 27, 30-33, 37-43, 57-60 and 64-70 of co-pending application 10/183,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 6-32 in the instant application disclose a medicinal composition comprising human OCIF protein or a homolog thereof and a polysaccharide; a method of enhancing the activity of a human OCIF protein or

homolog thereof by administering the OCIF protein and a polysaccharide; and a method for treating a bone-pathobolism comprising administering the composition. This is obvious in view of claims 1-3, 7-13, 27, 30-33, 37-43, 57-60 and 64-70 of the co-pending application which disclose a complex comprising at least one substance of OCIF, an analog thereof and a variant thereof, which is bound to at least one substance of a polysaccharide and a polysaccharide derivative; a pharmaceutical composition comprising the complex and a pharmaceutically active carrier; a method of prolonging the time that OCIF is retained in the bloodstream by administering the complex; and a method for the prophylaxis or treatment of bone metabolic diseases by administering the complex. Both sets of claims cite a medicinal composition comprising a human OCIF protein and a polysaccharide; a method of enhancing the activity of a human OCIF protein by administering the OCIF protein and the polysaccharide; and a method for treating a bone metabolic disease comprising administering the composition. Thus, claims 6-32 in present application and claims 1-3, 7-13, 27, 30-33, 37-43, 57-60 and 64-70 in the co-pending application are obvious variations of a medicinal composition comprising a human OCIF protein and a polysaccharide; a method of enhancing the activity of a human OCIF protein by administering the OCIF protein and the polysaccharide; and a method for treating a bone-pathobolism comprising administering the composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 6-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 7-13, 27, 30-33, 37-43, 57-60 and 64-70 of co-pending application 10/364,045. Although the conflicting claims are

not identical, they are not patentably distinct from each other because claims 6-32 in the instant application disclose a medicinal composition comprising human OCIF protein or a homolog thereof and a polysaccharide; a method of enhancing the activity of a human OCIF protein or homolog thereof by administering the OCIF protein or homolog thereof and a polysaccharide; and a method for treating a bone-pathobolism comprising administering the composition. This is obvious in view of claims 1-3, 7-13, 27, 30-33, 37-43, 57-60 and 64-70 of the co-pending application which disclose a complex comprising at least one substance of OCIF, an analog thereof and a variant thereof, which is bound to at least one substance of a polysaccharide and a polysaccharide derivative; a pharmaceutical composition comprising the complex and a pharmaceutically active carrier; a method of prolonging the time that OCIF is retained in the bloodstream by administering the complex; and a method for the prophylaxis or treatment of bone metabolic diseases by administering the complex. Both sets of claims cite a medicinal composition comprising a human OCIF protein and a polysaccharide; a method of enhancing the activity of a human OCIF protein by administering the OCIF protein and the polysaccharide; and a method for treating a bone metabolic disease comprising administering the composition. Thus, claims 6-32 in present application and claims 1-3, 7-13, 27, 30-33, 37-43, 57-60 and 64-70 in the co-pending application are obvious variations of a medicinal composition comprising a human OCIF protein and a polysaccharide; a method of enhancing the activity of a human OCIF protein by administering the OCIF protein and the polysaccharide; and a method for treating a bone-pathobolism comprising administering the composition.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 6-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a medicinal composition comprising human osteoclastogenesis inhibitory factor (OCIF) or non-precipitated human OCIF, or a defined homolog such as OCIF2, OCIF3, OCIF4 or OCIF5 and a defined polysaccharide such as heparin, dextran sulfate, pectin or carrageenan; a method of enhancing the activity of the OCIF or the homolog by administering the OCIF or the homolog and the polysaccharide; and a method for treating a specific bone-pathobolism such as hypercalcemia comprising administering the composition; or, a sustained-released composition comprising OCIF and a defined polysaccharide as indicated in the prior art, does not reasonably provide enablement for a medicinal composition comprising a homolog of human OCIF or non-precipitated human OCIF and a polysaccharide, a method of enhancing the activity of an OCIF homolog by administering the OCIF homolog and a polysaccharide, and a method for treating all diseases of bone-pathobolism comprising administering the composition comprising human OCIF or an OCIF homolog and a polysaccharide, where the homolog, the polysaccharide and the disease of bone-pathobolism are not defined or identified. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 6-32 are directed to a medicinal composition comprising human OCIF or non-precipitated human OCIF or a homolog thereof and a polysaccharide (claims 6-12 and 26-32); a method of enhancing the activity of OCIF or a homolog thereof by administering the OCIF or the homolog and a polysaccharide (claims 13-19); and a method for treating a bone-pathobolism comprising administering the composition (claims 20-25). The specification, however, only discloses cursory conclusions (pages 2-3) without data supporting the findings, which state that the present invention provides a bone-pathobolism treating agent comprising OCIF, its homologs, its variants and a polysaccharide or its derivative, in which the effect of OCIF on bone-patholism has been further increased and the effect has been rendered persistent. There are no indicia that the present application enables the full scope in view of a medicinal composition comprising OCIF or its homologs and a polysaccharide, and the use of composition to treat a bone-pathobolism as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the homologs of OCIF and the polysaccharides in the composition, and the diseases of bone-pathobolism, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification indicates a composition comprising OCIF and a polysaccharide such as heparin, dextran sulfate, pectin or carrageenan shows hypocalcemic effect in rat model, and the polysaccharide has enhance effect on persistence of OCIF (Examples 1-8; Figs 1-10), however, there are no other working examples indicating the claimed variants.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Goldenberg *et al.* (1998)) indicates a sustained-released composition containing a biologically active agent such as osteoprotegerin (OCIF), a hydrophilic polymer such as dextran sulfate, heparin or carrageenan, and at least one precipitating agent. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the use of the compositions containing various OCIF homologs and polysaccharides in the treatment of various bone metabolic diseases and the effects of the composition in the treatment to be considered enabling for the claimed variant.

(4). Predictability or unpredictability of the art:

The specification has shown a polysaccharide such as heparin, dextran sulfate, pectin or carrageenan can enhance the hypocalcemic effect of OCIF in rat model (Examples 1-10). However, the specification does not demonstrate the effect of a composition comprising OCIF or a OCIF homolog and a polysaccharide in treating various bone diseases, the invention is highly

unpredictable regarding the effect of the composition in the treatment. For example, the specification indicates heparin or dextran sulfate can enhance the hypocalcemic effect of OCIF, but the prior art (Chowdhury et al. 1992; Cochran et al., 1988) has shown heparin or other glycosaminoglycans can increase bone resorption. Thus, it requires further experimentation to assess the effect of the composition in the treatment of various bone metabolic diseases.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a medicinal composition comprising human OCIF or non-precipitated human OCIF or a homolog thereof and a polysaccharide; a method of enhancing the activity of OCIF or a homolog thereof by administering the OCIF or the homolog and a polysaccharide; and a method for treating a bone-pathobolism comprising administering the composition. The specification indicates certain known variants of OCIF and some known derivatives of polysaccharides can be used for treating bone-pathobolism (pages 3-7), and demonstrates a composition comprising OCIF and a polysaccharide such as heparin, dextran sulfate, pectin or carrageenan shows hypocalcemic effect in rat model, and the polysaccharide has enhance effect on persistence of OCIF (Examples 1-8; Figs 1-10). However, the specification has not demonstrated the treatment of various bone metabolic diseases such as osteoporosis and chronic articular rheumatism using a composition comprising OCIF or an OCIF homolog and a polysaccharide, nor has indicated the effect of the composition in the treatment. Furthermore, there are no working examples demonstrating the effects of these compositions. Since the specification fails to provide sufficient guidance on the use and effect of the composition containing OCIF or an OCIF homolog and a polysaccharide in treating various bone

metabolic diseases, it is necessary to carry out further experimentation to assess the effects of these compositions in the treatment.

(6). Nature of the Invention

The scope of the claims encompasses a medicinal composition comprising OCIF or an OCIF homolog and a polysaccharide; a method of enhancing the activity of OCIF or a OCIF homolog by administering a polysaccharide and the OCIF protein; and a method for treating a bone-pathobolism comprising administering the composition, but the specification does not demonstrate the use and the effect of the composition in the treatment of various bone metabolic diseases. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the effects of claimed composition in the treatment is unpredictable, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the compositions in the treatment of various bone metabolic diseases.

In response, applicants indicate the newly added claims clarify the compositions of inventions comprise both an OCIF protein and a polysaccharide; and the specification discloses a treating agent comprising OCIF or its variant (OCIF2, OCIF3, OCIF4, OCIF5) and a polysaccharide such as heparin, dextran sulfate, pectin or carrageenan (pages 6-7 of the response). The response has been considered, however, the argument is not fully persuasive because the specification discloses a composition comprising OCIF or a defined homolog and a defined polysaccharide such as heparin, dextran sulfate, pectin or carrageenan has hypocalcemic effect, but it does not indicate a medicinal composition comprising an undefined OCIF homolog

and a undefined polysaccharide, and the treatment of various bone diseases such as osteoporosis and chronic articular rheumatism using the composition comprising an OCIF protein and a polysaccharide as encompassed by the claims. Thus, the full scope of the claims is not enabled as indicated in the section above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 7-9, 15-17, 20-25 and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claims 7-9, 15-17, 21-23 and 27-29 are indefinite because of the use of the term "combinations thereof". Please note that Markush group recited in the claim requires closed language, however, the term "combinations thereof" indicates an open language as to which components and how much of each component being include in the combinations.

16. Claims 20-25 indefinite because the claim lacks essential steps as claimed in the process of treating a bone-pathobolism by administering a composition comprising a human OCIF protein and a polysaccharide. The omitted steps are the effective amount of the composition used and the outcome of the treatment. Claim 20 is also indefinite as to what subject is treated. Claims 21-25 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 6-9 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Goldenberg *et al.* (WO 98/46211, October 22, 1998).

Goldenberg *et al.* teach a sustained-released composition containing a biologically active agent such as osteoprotegerin (page 11, line 16; known as osteoclastogenesis inhibitory factor), a hydrophilic polymer such as dextran sulfate, heparin or carrageenan (page 7, lines 24-page 8, line 17; claims 6-9 and 12), and at least one precipitating agent (page 5, line 23-page 6, line 1). The term "for treating a bone-pathobolism" is an intended use, which does not play weight in the claimed composition.

In response, applicants indicate Goldenberg *et al.* provide a long list of biologically active agents and a long list of hydrophilic polymer, from which one can choose one biologically active agent and one hydrophilic polymer and combined them with at least one precipitating agent, and it is Examiner's contention that since Goldenberg *et al.*'s long list biologically active agents includes OCIF, thus the claimed composition comprising OCIF and a polysaccharide is anticipated, which would create an improper "hindsight" anticipation; and Goldenberg *et al.* teach the biologically active agent is co-precipitated with the hydrophilic polymer to form a matrix of the precipitated polymer and agent, while the claimed invention is directed to

administer a non-precipitated mixture of OCIF and a polysaccharide to a subject, the biological activity of OCIF is enhanced by the polysaccharide, and Goldenberg *et al.* do not disclose such effect with the composition (pages 9-10 of the response). The response has been fully considered, however, the argument is not found persuasive because the biologically active agents cited by Goldenberg *et al.* including OCIF are known biologically active peptides and have been used for preparing pharmaceutical compositions, thus the combination of one specific agent such as OCIF and a polysaccharide would be expected in view of the reference. Regarding the difference between the two compositions of Goldenberg *et al.* and the claimed invention cited by applicant, the argument is also not found persuasive because the limitation on the difference is not cited in the claim, thus, the claimed invention does not exclude the matrix composition of Goldenberg *et al* and is anticipated by the reference.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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October 3, 2003

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